# USE OF RITUXIMAB COMPARED TO ANTI-TNF AGENTS AS SECOND AND THIRD LINE THERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS. A REPORT FROM THE RHUMADATA® CLINICAL DATABASE AND REGISTRY

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## INTRODUCTION

The order of use of biologic agents after failing a TNF inhibitor is still a question for debate. Phase III trial data in TNF-IR patients show comparable efficacy results across biologic agents and limited head-to-head studies have been published. Prospective registries offer a unique opportunity to observe the effectiveness (combined evaluation of efficacy and safety profile over time) of these agents in a clinical setting.

## OBJECTIVES

To evaluate if patients with rheumatoid arthritis (RA) treated with rituximab (RIT) after failing a first or a second anti-TNF agents (TNF-IR) have a different drug retention rate than patients similarly prescribed anti-TNF agents (pooled adalimumab, etanercept or infliximab) and compare the treatment strategies of using RIT as second or third biologic treatment.

## METHODS

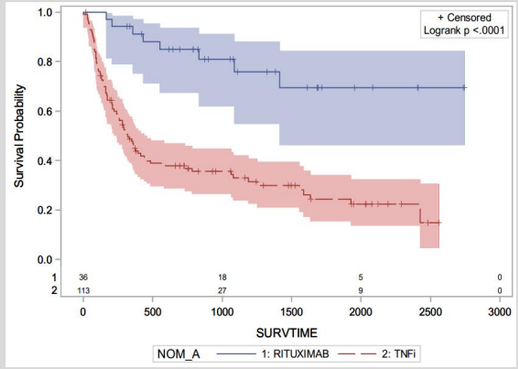
Data from TNF-IR RA patients prescribed adalimumab (ADA), etanercept (ETA), infliximab (INF) or rituximab (RIT) as second or third biologic agents on or after January 1st 2007 was extracted and subjects taking either ADA, ETA or INF were pooled to form the anti-TNF cohort. Baseline demographics included age, disease duration, HAQ-DI, fatigue and pain visual analog scale evaluations (VAS), TJC, SJC, DAS 28 ESR and SDAI. Five-year drug retention rates were estimated and compared using Kaplan-Meier survival estimates. Statistical analysis was performed using SAS version 9.3. RHUMADATA® is a clinical database and registry used in daily clinical practice at the IRM and CORQ.

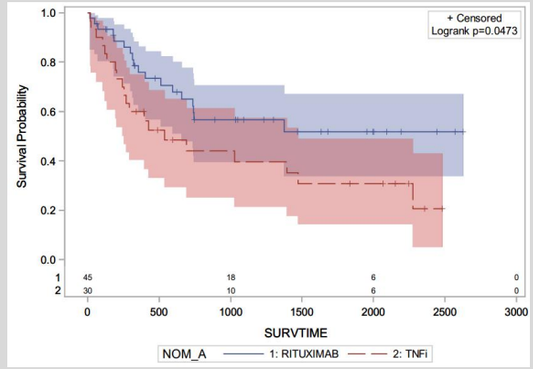
## BASELINE CHARACTERISTICS

| | Second biologic agent | | | | | |
|---|---|---|---|---|---|---|
| | ADA | ETA | INF | RIT | p-value | ALL |
| N | 49 | 45 | 19 | 36 | | 149 |
| Age (years)* | 51.0 (15.1) | 57.3 (15.0) | 50.6 (18.0) | 58.6 (9.0) | 0.0328 | 54.7 (14.6) |
| Women (%) | 69.4% | 77.8% | 63.2% | 66.7% | 0.5890 | 70.5% |
| Disease duration (years) | 10.7 (7.5) | 10.9 (9.5) | 7.8 (7.8) | 12.9 (9.6) | 0.2466 | 10.9 (8.7) |
| Number of previous DMARDs | 2.7 (1.1) | 2.6 (0.9) | 2.6 (1.3) | 2.9 (1.1) | 0.5149 | 2.7 (1.1) |
| Previously used DMARDs | | | | | | |
| Methotrexate | 96% | 96% | 95% | 97% | | 96% |
| Hydroxychloroquine | 65% | 80% | 79% | 83% | | 76% |
| Leflunomide | 43% | 40% | 47% | 47% | | 44% |
| Sulfasalazine | 27% | 18% | 21% | 19% | | 21% |
| Number of current DMARDs | 1.3 (0.5) | 1.2 (0.4) | 1.3 (0.4) | 1.2 (0.5) | 0.6251 | 1.2 (0.4) |
| Currently used DMARDs | | | | | | |
| Methotrexate | 55% | 49% | 68% | 64% | | 57% |
| Hydroxychloroquine | 22% | 29% | 26% | 22% | | 25% |
| Leflunomide | 6% | 4% | 11% | 11% | | 27% |
| Sulfasalazine | 4% | 2% | 0% | 3% | | 16% |
| HAQ-Score (0-3) | 1.2 (0.8) | 1.3 (0.6) | 1.3 (0.8) | 1.4 (0.5) | 0.6791 | 1.3 (0.6) |
| Fatigue (VAS, 0-10) | 4.4 (4.0) | 4.2 (3.3) | 4.3 (3.2) | 5.0 (3.0) | 0.8081 | 4.5 (3.4) |
| Pain (VAS, 0-10) | 4.9 (3.5) | 4.5 (3.4) | 4.1 (2.8) | 5.2 (3.1) | 0.7175 | 4.7 (3.2) |
| CRP (mg/L) | 16.2 (24.4) | 6.9 (11.4) | 14.8 (28.6) | 15.7 (18.8) | 0.1405 | 13.0 (20.6) |
| ESR (mm/hr) | 22.7 (16.7) | 21.3 (21.5) | 25.3 (27.3) | 29.4 (28.1) | 0.4302 | 24.3 (22.9) |
| RF+ (%) | 64.1% | 65.8% | 46.7% | 90.9% | 0.0088 | 69.6% |
| anti-CCP+ (%) | 62.5% | 46.4% | 63.6% | 100.0% | 0.0016 | 66.7% |
| Tender joint count (TJC, 0-28) | 4.2 (5.5) | 6.1 (5.6) | 5.9 (7.2) | 6.6 (7.4) | 0.5644 | 5.7 (6.3) |
| Swollen joint count (SJC, 0-28) | 5.2 (4.9) | 6.3 (5.8) | 5.5 (6.0) | 7.8 (6.4) | 0.4033 | 6.3 (5.8) |
| physician GLOBAL (VAS, 0-10) | 2.2 (2.3) | 2.3 (2.5) | 3.5 (3.5) | 2.0 (2.8) | 0.5266 | 2.3 (2.6) |
| patient Global (VAS, 0-10) | 4.2 (3.3) | 3.8 (2.9) | 3.8 (2.7) | 5.3 (2.7) | 0.2292 | 4.3 (3.0) |
| CDAI | 15.8 (10.0) | 19.7 (14.2) | 18.9 (16.8) | 23.3 (15.1) | 0.3537 | 19.5 (13.8) |
| DAS28-4(ESR) | 3.5 (1.1) | 3.7 (1.4) | 3.4 (1.8) | 4.1 (1.4) | 0.4196 | 3.7 (1.4) |

* Data are presented as means (SD), unless stated otherwise.

| | Third biologic agent | | | | | |
|---|---|---|---|---|---|---|
| | ADA | ETA | INF | RIT | p-value | ALL |
| N | 13 | 7 | 10 | 45 | | 75 |
| Age (years) | 56.1 (15.2) | 46.1 (11.3) | 53.5 (11.5) | 57.0 (11.4) | 0.1736 | 55.3 (12.3) |
| Women (%) | 92.3% | 85.7% | 80.0% | 80.0% | 0.7622 | 82.7% |
| Disease duration (years) | 13.1 (9.3) | 14.1 (9.4) | 6.9 (5.6) | 14.3 (9.9) | 0.1693 | 13.1 (9.5) |
| Number of previous DMARDs | 3.5 (1.2) | 2.3 (0.8) | 2.8 (1.1) | 3.0 (1.2) | 0.1639 | 3.0 (1.1) |
| Previously used DMARDs | | | | | | |
| Methotrexate | 100% | 100% | 100% | 98% | | 99% |
| Hydroxychloroquine | 85% | 71% | 80% | 78% | | 79% |
| Leflunomide | 69% | 29% | 60% | 51% | | 53% |
| Sulfasalazine | 38% | 14% | 20% | 36% | | 32% |
| Number of current DMARDs | 1.3 (0.5) | 1.3 (0.5) | 1.4 (0.5) | 1.3 (0.5) | 0.8656 | 1.3 (0.5) |
| Currently used DMARDs | | | | | | |
| Methotrexate | 31% | 86% | 70% | 64% | | 84% |
| Hydroxychloroquine | 8% | 29% | 30% | 31% | | 32% |
| Leflunomide | 0% | 0% | 20% | 9% | | 11% |
| Sulfasalazine | 0% | 0% | 10% | 4% | | 4% |
| HAQ-Score (0-3) | 1.4 (1.0) | 1.4 (0.9) | 1.3 (0.8) | 1.5 (0.6) | 0.9036 | 1.5 (0.7) |
| Fatigue (VAS, 0-10) | 4.6 (4.1) | 6.1 (3.7) | 6.3 (2.3) | 5.7 (3.3) | 0.8154 | 5.7 (3.3) |
| Pain (VAS, 0-10) | 4.5 (3.7) | 5.9 (1.8) | 8.1 (1.0) | 6.2 (3.5) | 0.3396 | 6.1 (3.3) |
| CRP (mg/L) | 6.2 (9.0) | 3.9 (1.7) | 10.7 (20.8) | 19.3 (28.0) | 0.2283 | 14.7 (24.1) |
| ESR (mm/hr) | 18.8 (15.1) | 21.9 (17.2) | 26.0 (34.5) | 32.7 (31.5) | 0.4563 | 28.4 (28.3) |
| RF+ (%) | 54.5% | 40.0% | 0.0% | 89.7% | <.0001 | 70.5% |
| anti-CCP+ (%) | 60.0% | 50.0% | 25.0% | 72.0% | 0.3163 | 63.9% |
| Tender joint count (TJC, 0-28) | 6.4 (5.5) | 4.4 (4.0) | 8.3 (4.3) | 7.2 (7.0) | 0.9884 | 6.9 (6.3) |
| Swollen joint count (SJC, 0-28) | 7.3 (4.0) | 4.0 (2.3) | 8.5 (2.1) | 8.0 (6.5) | 0.8714 | 7.5 (5.7) |
| physician GLOBAL (VAS, 0-10) | 2.8 (3.4) | 3.4 (3.3) | 4.3 (3.3) | 3.1 (3.2) | 0.6173 | 3.2 (3.2) |
| patient Global (VAS, 0-10) | 3.9 (3.4) | 6.6 (2.3) | 6.8 (1.1) | 5.5 (3.2) | 0.2881 | 5.5 (3.0) |
| CDAI | 19.9 (11.6) | 17.8 (11.0) | 25.7 (6.1) | 24.2 (11.4) | 0.9617 | 22.8 (11.0) |
| DAS28-4(ESR) | 4.0 (1.3) | 3.6 (1.2) | 4.0 (0.6) | 4.0 (1.3) | 0.8942 | 4.0 (1.2) |




## RESULTS

The data from 224 RA patients were extracted, 149 and 75 having respectively failed a first and a second anti-TNF agent. No clinically significant differences in baseline variables were observed between treatment groups in second and third intention. The 5 year retention rates of second line RIT and anti-TNF use were 70% and 24% respectively (Log-rank p<.0001). In patients having failed two anti-TNF, subsequent use of RIT and anti-TNF agents respectively demonstrated 5 year retention rates of 52% and 31% (Log-rank p=0.0473). Although numerically superior (70% vs 52%) second line use of RIT did not reach statistical difference when compared to third line usage (Log-rank p=0.0536).

## CONCLUSIONS

As a second line agent, in TNF-IR patients, RIT demonstrates a better 5 year retention rate than anti-TNF agents. As third line therapy, RIT is also statistically superior to anti-TNF agents. Although no statistical difference was demonstrated between second and third line RIT use, it is evident that positioning RIT as second line offers a better long term outcome.

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